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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/924,654	08/07/2001	Richard D. Goold	PC-0049 CIP	7397

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 09/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,654	GOOLD ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

The Amendment filed June 16, 2003 (Paper No. 9) in response to the Office Action of March 17, 2003 is acknowledged and has been entered.

Claims 1-15 are pending.

Claims 5-15 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-4 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections/Objections Withdrawn:

The objections and rejections made in Paper No. 8 are withdrawn in view of applicant's amendments and arguments thereto.

New Objections/Rejections:

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 2 is drawn to an antigenic

epitope of the protein of Claim 1 comprising residues 550-565 of SEQ ID NO:4. Due to the open language, Claim 2 also reads on an antigenic epitope comprising SEQ ID NO:4 since SEQ ID NO:4 "comprises" residues 550-565. This objection can be obviated by amending the claims to an antigenic epitope of the protein of Claim 1 consisting of residues 550-565 of SEQ ID NO:4. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a purified protein (or composition thereof) comprising an amino acid sequence of SEQ ID NO:4; an antigenic epitope of the protein of Claim 1 comprising residues 550-565 of SEQ ID NO:4; and a biologically active portion of the protein of Claim 1 consisting of residues 404-417 of SEQ ID NO:4.

The claims are not enabled because the specification fails to enable any person skill in the art to which it pertains how to use the claimed protein in any predictable manner either for diagnostic or therapeutic purposes.

For example, the specification contemplates (page 6, line 5) that the claimed protein may be used to treat a subject with cancer. The specification further contemplates that the purified protein may be used to generate polyclonal and or monoclonal antibodies which bind specifically to the protein to form an antibody-protein complex, the formation of which when compared to standards is diagnostic of cancer (page 7, lines 2-3). To substantiate these uses, the inventors have asserted that the **polynucleotide** (SEQ ID NO:3) *encoding* the protein of SEQ ID NO:4 is a "tumor suppressor" gene. Differential expression of SEQ ID NO:3 (page 12, lines 17-30) in ovary tumor cells compared to normal ovary cells revealed a lower fractional abundance of SEQ ID NO:3. Further, via transcript imagining, the inventors assert that SEQ ID NO:3 is diagnostic of prostate cancer (page 36, line 17), ovarian cancer (page 37, line 15) and pancreatic cancer (page 37, line 26).

However, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict proportionate levels of polypeptide translation. It is well known in the art that the basic molecular biology of eukaryotic gene transcription is tightly regulated. For example, Alberts *et al.* (Molecular Biology of the Cell, 3rd

edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is "blocked" during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferin receptor polypeptide is translated. Also, with regards to tumor suppressor genes, Fu *et al.* (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Furthermore, Rama *et al.* (Biochem. J. Vol. 318, 1996, pages 333-341) teach that the glucocorticoid, betamethasone, increased mRNA expression of cholinephosphate cytidylyltransferase (CT) as determined by RT-PCR and Southern analysis, but did not alter the levels of the CT enzyme as assayed by Western blotting (abstract, and page 339, 2nd column, 2nd paragraph). Thus, the predictability of protein translation and its possible use as a diagnostic are not contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Furthermore, if a protein such as SEQ ID NO:4 is to be used as a surrogate for a disease state, some disease state must be identified in some way with the protein, and not just the polynucleotide transcript. For example, the specification specifically teaches (page 37, line 30) in assays using normal and cancerous standards and patient samples, an antibody specifically binding the protein "serves as a clinically relevant diagnostic marker for breast, ovary, pancreas, or prostate cancer". However, as seen in the state of the art above, one needs to know, e.g., that the claimed protein is present only in cancer tissue to the exclusion of normal tissue (or vice versa). Thus, in the absence of any correlation between the claimed protein with any known disease or disorder, any information obtained from various expression profiles in both normal and diseased tissue only serves as the

basis for further research on the observation itself. Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would not be able to predictably use the protein of SEQ ID NO:4 in any diagnostic setting without undue experimentation.

Further, with regards to the use of the protein in treating cancer, the specification teaches (page 21, lines 12-15) that in one embodiment, a cancer which has decreased expression of the protein may be treated by the delivery of the protein or a pharmaceutical composition comprising the protein. However, the specification fails to provide sufficient guidance and or objective evidence to one of skill in the art that the protein will predictably function as a therapeutic.

In general, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, Bellone *et al.* (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk

of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the protein in any diagnostic manner and or therapeutic formulation as contemplated. Thus, it would require undue experimentation by one of skill in the art to use the invention as claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
September 1, 2003